HIGHLIGHTS OF THE YEAR

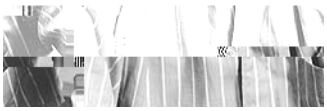
The research and education programs at the Laboratory continue their strong momentum. The Watson School of Biological Sciences recruited its second class of students this year, and the DNA Learning Center underwent extensive renovations that will further its educational objectives. The Meetings and Courses program and Banbury Center continue to be invaluable resources for scientific information, and the Cold Spring Harbor Laboratory Press added new projects and properties to its long list of titles. In this, the year of the Human Genome, Cold Spring Harbor Laboratory was a bustling center of scientific activitHtPQfZP.WHUXWTXHYHXHUYVHP examining how Apaf-1 acts in concert with an enzyme called caspase-9 to trigger the cell death machinery.

Scott Lowe

RNA Splicin an rea Cancer

In 1977, CSHL scientist Richard Roberts and his colleagues published a pap began “An amazing sequence arrangement…” Rich’s use of the adjective “a serious scientific article was highly unusual and strangely prescient, becau reported a discovery for which he would later win the Nobel prize. A number o Cold Spring Harbor Laboratory and MIT published the discovery that genes a contiguous, but rather occur as blocks of relevant coding sequences (later calle are interspersed with blocks of intervening, noncoding sequences (introns).

Introns are removed at the level of RNA by a splicing mechanism. This year, Adrian Krainer and his colleagues discovered why particular mutations in the *CA1* gene alter premessenger RNA splicing and thereby predispose individuals to breast and ovarian cancer.



Adrian Krainer

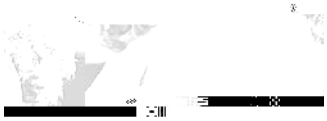
Although complex in detail, the basic splicing mechanism involves cutting a premessenger RNA molecule at two sites (the splice junctions), discarding the intron thus released, and joining the exons together. This basic splicing mechanism is mediated by the binding of splicing factors to the splice junctions and the action (e.g., cutting and joining) of splicing factors at these sites. Recently, however, additional sites that stimulate splicing have been identified within exons. These sequences are called *e*xonic *s*plicing *e*nhancers or ESEs. Adrian and his CSHL bioinformatics colleague Michael Zhang have developed rules for predicting the presence of ESEs within genes of particular interest. They discovered that a mutation in the *CA1* gene—known to alter splicing and predispose individuals to breast and ovarian cancer—disrupts an ESE. In addition, Adrian found that disruption of ESE function may contribute to many other diseases, including cystic fibrosis, neurofibromatosis, Wiskott-Aldrich syndrome, and Menkes disease.

apill a ir NA Replica i n an Cer ical Cancer

DNA contains specialized regions—called origins of replication—that enable the stable "seal" between the two strands of the double helix to be broken. This breaking of the seal between the strands of DNA is the first step in DNA replication, the process that copies DNA. It results from the action of enzymes called DNA helicases that bind to origins of replication and unwind the DNA. Arne Stenlund is investigating how the DNA helicase of papillomavirus binds to the origin of replication in the viral genome and initiates the unwinding of viral DNA prior to DNA replication, a process necessary for the virus to multiply and spread. Papillomaviruses are a family of DNA tumor viruses that infect mammals and cause both benign and malignant epithelial tumors such as polyps and cancer of the cervix. Virtually all human cervical cancer can be attributed to papillomavirus infection. Therefore, the papillomavirus DNA helicase is an attractive target for antiviral drugs and other treatment strategies.

Arne Stenlund

Arne, together with Grace Chen (now at the University of Michigan Medical School), found that a complex mechanism governs how the papillomavirus DNA helicase works. The enzyme, made up of a protein called E1, binds to the viral origin of replication by nestling up to another papillomavirus protein, E2. Together, these proteins bind to adjacent sites at the origin, where E1 then becomes an active DNA helicase and begins to unwind the double helix. Arne and Grace have discovered that E2 acts as a loading factor that deposits E1 on a specific sequence of DNA, the papillomavirus origin of replication.



Leemor Joshua-Tor

Using X-ray crystallography, Leemor Joshua-Tor and postdoctoral fellow Eric Enemark have determined the three-dimensional structure of a part of E1 that binds to DNA and to E2. By obtain-

ing a detailed view of E1's biochemical properties and structure, Arne and Leemor have uncovered interesting clues about how the papillomavirus DNA helicase is put together, how it functions, and what steps might be taken to block the function of this enzyme as a way to prevent cervical cancer.

Ne r cience

Brain ● *n* How does a single cell—a fertilized egg—become a complex organism composed of billions of cells of thousands of different kinds? How do cells arise at the correct time and place during the development of an organism and adopt the specialized characteristics that make them bone, muscle, or nerve? How is cell number controlled so that tissues, organs, and body parts adopt the correct size? Regulated transitions from cell proliferation to cell differentiation—during which cells stop growing and adopt specialized characteristics—are the key to these phenomena.

Since 1992, Grigori (Grisha) Enikolopov has made a series of important discoveries concerning how the biochemical messenger nitric oxide (NO) instructs the cells in a developing organism to stop dividing, enabling them to differentiate into specialized cell types. Building on that research, Natalia (Natasha) Peunova, Hollis Cline, and Grisha found that experimentally altering NO levels in the developing brain of tadpoles significantly affects brain

Using “two-photon” microscopy (a high-resolution imaging technique whose application to neuroscience Svoboda pioneered), Karel and postdoctoral fellow Bernardo Sabatini watched calcium flow into single dendritic spines of electrically stimulated brain neurons. These measurements enabled Karel and Bernardo to determine the number and type of “calcium channels” present at synapses in a region of the brain important for learning and memory, the hippocampus. Calcium channels are molecular gates that open in response to electrical stimulation and allow calcium to flow into dendritic spines. Once inside, calcium triggers biochemical events in the spine that modify synaptic strength.

The strengthening of synapses between neurons in response to experience is believed to underlie complex brain functions such learning and memory. Karel, Robert Malinow, and several other CSHL neuroscientists have made a series of significant discoveries about this process. Visualizing how neurons communicate with each other on the most basic level, as Karel has done by imaging calcium, provides important clues for understanding how our brains outperform the most sophisticated computers and, in so doing, enable us to grasp the human experience.

T e re ical an C p a i nal Ne r cience

The discoveries made by traditional neuroscientists result from experiments with living tissue. In contrast, theoretical and computational neuroscientists use mathematics to describe how the brain works. Much of Dmitri (Mitya) Chklovskii’s theoretical neuroscience research is based on the idea that biology and evolution impose several design constraints on the structure of the nervous system. For example, scientists have long believed that neurons are positioned and connected in the brain in such a way as to minimize the length—and hence the volume—of wiring.

Mitya has developed a mathematical formulation of this “wiring economy” principle that enables several predictions to be made about how neurons are connected to each other in the brain. Mitya’s “wire length minimization” model corresponds closely with the observed properties of the mammalian visual cortex, a brain region that processes visual information. The human brain contains approximately 300 million feet of wiring packed into a 1.5-quart volume, but the brain would be much larger if it did not employ the strategy Mitya has uncovered for fitting the necessary wiring into the available, limited space.

Recently, Mitya has turned his efforts to understanding the neurological basis of optical illusions. By determining what happens when the brain is tricked, e.g., by an optical illusion, Mitya aims to uncover new principles of brain function.

lan lec lar i l an ene ic

Owing to its small size and short generation time (~6 weeks from seed to adult), the mustard relative *Arabido sis thaliana* has

become a workhorse of plant molecular biology and genetics. In addition to pursuing their specific research interests, W. Richard McCombie and Robert Martienssen helped organize the *Arabido sis* Genome Initiative, a large-scale international effort established in 1996 to sequence the entire genome of this plant species.

This year, and well-ahead of schedule, the *Arabido sis* Genome Initiative reached its goal of sequencing the entire *Arabido sis* genome and thus obtained the first-ever complete genome sequence from a plant. This achievement has profound implications for biology, medicine, agriculture, and the environment because it will enable detailed studies of the entire genetic structure of plants to be carried out. Such studies will yield a great deal of new information about plant growth; crop yields; disease and drought resistance; ripening and spoilage; pharmaceutical, vitamin, and "edible vaccine" production; and many other aspects of plant biology.

S s L

From May 31 to June 5, biologists from a number of research fields gathered for the 65th annual CSHL Symposium, this year titled "Biological Responses to DNA Damage." On Sunday, June 4, meeting attendee Jan H.J. Hoeijmakers of Erasmus University in Rotterdam delivered the annual Dorcas Cummings Memorial Lecture to a scientific and public audience, a very successful annual event hosted by the CSHL Association.

appointment follows Winship Herr's seven-year role as an energetic and very effective Deputy Director. Winship has stepped down to focus on the development of the Watson School (for which he serves as Dean) and his other duties as Assistant Director of the Laboratory.

Denise Roberts, the Laboratory's new Research Administrator, has also assumed the administrative duties for the Cancer Center.

• a s Sch , ca Sc e ces

CSHL's graduate school—the Watson School of Biological Sciences—welcomed its second class of students this fall. On August 28, nine new students joined the Watson School's ranks, the second class to enter the program. Hailing from across the country and around the world, the students dove quickly into their rigorous programs, enrolling in the core courses and beginning the laboratory rotations that mark their first year of study.

Honorary Board of Trustees member David L. Luke III continues to lead the fund-raising efforts to fully fund the Watson School programs. This year, nearly $7 million was raised to support the Watson School, its graduate program, and its students.

Pres e a E e s

James D. Watson, president of CSHL, has had another busy year, most recently promoting his newest book, *A assion for NA: enes, enomes, and Society*. The collection of essays, published by the CSHL Press, was nationally publicized through an exhausting 4-month book tour. Locally, Jim was a big hit at Huntington's Book Revue, where hordes of fans lined up for the Nobel Laureate's autograph. Jim was also honored on July 4 with the prestigious Philadelphia Liberty Medal. Jim received the award, together with Francis H.C. Crick, for the "tremendous impact of their science on our lives and public policies."

Lewis Miller, an Australian artist and winner of the prestigious Archibald Prize—Australia's premier award for portraiture—returned to CSHL for a month this summer. Miller, who visited the Laboratory during the 1998 Symposium to sketch attendees and Laboratory personnel, has many works exhibited throughout Blackford Hall. His mission this summer was more specific: I commissioned Miller to paint a full-sized portrait of James D. Watson.

James Watson meets young fans while promoting *A assion for NA.*

Miller's efforts were a success: A seven-foot representation of CSHL's President now hangs in a place of honor inside Grace Auditorium, where Jim has spent countless hours lecturing to public and scientific audiences. While at the Laboratory, Miller also completed several other portraits, including sketches of Charles and Helen Dolan, long-time supporters of the Laboratory. Mrs. Dolan, who currently serves on the Laboratory's Board of Trustees, was particularly pleased with the charcoal drawings Miller presented to the couple. In all, Miller completed more than 15 portraits while at the Laboratory, and each was framed for display around the Laboratory campuses.

3 h A ersar Re s Yeas C rse

Since the inception of CSHL's Yeast Genetics Course 30 years ago, nearly 500 scientists from around the world have traveled to Cold Spring Harbor to learn more about this relatively simple organism. Although simple in structure, yeast undergoes many of the complex biological processes of higher-order organisms, making it a model system for the study of molecular biology. CSHL's Yeast Genetics Course has helped to elevate yeast to its present "stardom," and most of the outstanding yeast geneticists/molecular biologists of the past half-century have either taken the course, taught the course, or both.

To celebrate the great science and lifelong friendships that have resulted from the Yeast Genetics Course, the Laboratory held a reunion for course participants on August 11. The event brought together students and instructors of the course—both past and present—for 2 days of reminiscing and sharing of current research. The reunion illustrated the influence that the course has had on its participants, as well as the impact that these investigators have had on science. "lsXsciencn sePsRaginPhave wPhigmorQYePe wQYePbsciencn'eciencn display wH[Pest

visitor to have been immortalized by Hollywood, when he was played by Robin Williams in the film *Awakenings*, based on his book. Howard Gardner spoke on his theory of multiple intelligences, and there was a spirited discussion of human intelligence following a presentation by Charles Murray, coauthor of *The ell Curve*. Participants were treated to appearances by Alex the African Gray Parrot (by Irene Pepperberg) and, at the other extreme, robots (by Howard Gardner). In between, Stephen Pinker discussed his ideas on language, while Vilayanur Ramachandran reviewed the neuropsychological basis of sensory perception. We are grateful to David Deming of J.P. Morgan for helping us to present such an extraordinary meeting.

drive of this institution. This year, the Board welcomed the addition of Jacob Goldfield, a private investor.

The Board of Trustees bid a fond farewell to two long-standing Board members, Martha Farish Gerry and John J. Phelan. Mrs. Gerry has served on the Board for more than 10 years, serving on the Banbury Program, Building, DNA Learning Center, and Development Committees; she was also Secretary of the Board from 1997 to 2000. Mr. Phelan, who led the Board's Commercial Relations Committee since 1996, served the Laboratory for more than 8 years and was also represented on the Board's Audit and Executive Committees. Both Trustees were honored at the Board's November 4 meeting for their outstanding service and unwavering loyalty to Cold Spring Harbor Laboratory.

CSHL Ass c a

The CSHL Association (CSHLA) held its annual meeting on February 5, 2000. The membership honored its retiring directors, including Mary Ann Charlston and Mary D. Lindsay (who was simultaneously named an Honorary Director). The Association also elected several new directors, including William F. Gerry, Lynn M. Gray, Susan Hollo, and Allen Dulles Jebsen. George W. Cutting, Jr., a former president of the CSHLA and a former honorary director, was reelected and returned as an active director this year.

The annual meeting also featured a lecture by Dr. Steven Pinker, Professor of Psychology in the Department of Brain and Cognitive Sciences at the Massachusetts Institute of Technology. His lecture, titled "Words and Rules: The Ingredients of Language," discussed the components and importance of human communication.

On April 15, 2000, the Association hosted *Jazz at the L*

a r G s

2000 was an exciting year for fund-raising. Several major campaigns continue to be successful: the campaign to fund the new Genome Research Center; the BioMedia Addition to the DNA Learning Center; and a continuing campaign for the Watson School of Biological Sciences. Results for all were astounding, and we are very fortunate to have such generous and supportive friends at Cold Spring Harbor Laboratory.

T e en e Re earc Cen er

As the Genome Research Center in nearby Woodbury nears completion, the fund-raising effort to support this new facility is already under way. A pledge of support was made by Mrs. Joy Levy, wife of the late Senator Norman J. Levy, who has offered to make the Genome Research Center the beneficiary of the efforts of the Norman J. Levy Foundation. To start the process, Mrs. Levy has pledged $250,000; her brother and sister-in-law, Jerry and Linda Saslow, have pledged $50,000 as well. The William & Maude Pritchard Charitable Trust has made a gift of $280,500 to support the Genome Research Center, and Arrow Internet

PE Biosystems made a gift-in-kind of $130,570 to furnish the addition with equipment, and Mr. and Mrs. Denis J. O'Kane made a generous gift of $35,000 to further fund the facility. The New York Stock Exchange also made a gift of $10,000 to the project.

Translational Science

rea Cancer S pp r

A new decade did nothing to hamper the efforts of the numerous breast cancer groups who support the Laboratory's cancer program.

1 in 9: The Long Island Breast Cancer Action Coalition—which celebrated 10 years of

disorders that may have a genetic basis identical to disorders of human beings. But perhaps the most fascinating feature of dogs is their behavior. Raymond Coppinger (Hampshire College) has specialized in studies of the behavior of working dogs, and he described the differing characteristics of the sheepdogs that guard flocks and those that herd flocks. All-in-all, the speakers introduced us to a wonderful blend of science and our everyday experiences of the animal that has been associated with human beings for at least 14,000 years.

Ga r e s Fe

Douglas A. Melton, Ph.D., of the Howard Hughes Medical Institute and the Department of Molecular and Cellular Biology at Harvard University was the Laboratory's sixth Gavin Borden Visiting Fellow. Dr. Melton's lecture, titled "Construction of the Pancreas," was held on October 2 in Grace Auditorium. The Lecture series was named in memory of Gavin Borden, a science writer whose work on *Molecular iology of the Cell* and several other books made a lasting impression on the Laboratory.

Pr ec s

The historic landscape of Cold Spring Harbor Laboratory changed again this year, with the completion of three new building projects. On May 3, the Laboratory dedicated the Samuel Freeman Building, located adjacent to Urey Cottage. The Freeman Building—part of the Laboratory's neuroscience program—is a state-of-the-art facility for neuroscientists who use computer technologies to aid in the study of the brain. The building was made possible

Murray. The building, designed by Jim Childress of Centerbrook architects, is an Adirondack-style structure, accented by dark wood siding and a gabled roof of copper-foil-coated shin-

The objective of the program is to provide a greater understanding of the principles of biology. It instills in the students an awareness of major topics of investigation, helps develop intellectual tools necessary for modern research, exposes students to the process of research, and allows them to meet the top scientists who visit CSHL.

The program received financial support in 2000 from the C. Bliss Memorial Fund, the Burroughs Wellcome Fund, Robert Cummings, Dr. Ira Herskowitz, the Jephson Educational Trust, the JM Foundation, the National Science Foundation, and the URP Endowment Fund (composed of the Emanual Ax Fund, the Garfield Fund, the Glass Fund, the Libby Fund, the Olney Fund, the Read Fund, the Shakespeare Fund, and the Von Stade Fund).

Par ers r he F re

C O reach

Grateful for the overwhelming support that CSHL receives, a number of employees set out this year to “give back” to the Long Island community.

- CSHL “road-runners” were on-hand at the Cigna 5K Walk/Run, to support 1 in 9: The Long Island Breast Cancer Action Coalition, held at Eisenhower Park in East Meadow on August 24. The CSHL group is grateful for more than 10 years of support from 1 in 9. Lynn Cannon, Administrative Assistant in the Development Office, came in third for her age group in the run. In all, the event raised more than $100,000.
- Members of the W. Richard McCombie lab made a generous contribution to the North Shore Pediatric Oncology Unit to purchase holiday gifts for the patients. In their certificate of appreciation, administrators at North Shore noted how the gifts really touched the children.

S ec a E e s

Ne r cience ec re Serie

This year, the Laboratory continued a series of public education lectures by hosting its first Neuroscience Lecture Series. The three public lectures attracted more than 900 visitors to Grace Auditorium. The first lecture was given by Dr. Michael Merzenich on November 14, titled “Training Strategies for Brain Illnesses and Disabilities in Children.” Dr. Merzenich is the Francis A. Sooy Professor of Otolaryngology at the Keck Center for Integrative Neurosciences at the University of California, San Francisco. The second lecture, held November 21, was given by Dr. Charles F. Stevens, a professor from The Salk Institute for Biological Sciences. Dr. Stevens’ lecture was titled “Synapses: The Neural Information Highway.” The final lecture in the series was given by Dr. Larry Squire, Professor of Psychiatry and Neurosciences at the University of California School of Medicine in San

er ec re

Cold Spring Harbor Laboratory continued to host the Huntington Hospital Lecture Series, which ran from February to June. This year's topic was "Keeping Your Heart Healthy," part of Huntington Hospital's Heart Health Lecture program.

On June 26, the Laboratory welcomed Viviana Risca, the 2000 winner of the Intel Science Talent Search, and Laura F. Landweber, an assistant professor at Princeton University, for a special public lecture on "DNA Games: From Computing to Espionage." The event attracted a large group of teens and adults interested in DNA and the human genome.

On October 28, Phillip Valentine Tobias, Professor Emeritus at the University of the Witwatersrand in Johannesburg, presented a special public lecture titled "Humanity's Cradle: 75 Years of Evolutionary Studies in Africa." As part of a special Halloween program, "Bones and Strings," Dr. Tobias lectured on his research of the human biology of the peoples of Southern Africa. A special public concert by famed violinist Viviane Hagner followed the lecture.

C ncer

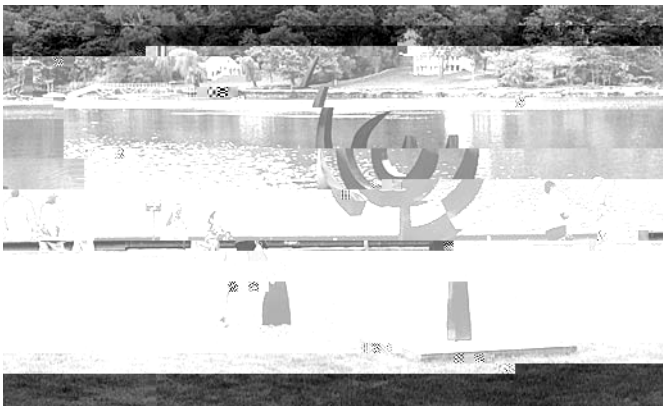
As part of the Laboratory's Millennium Cultural Series, several concerts were held this year. Attended by the participants of CSHL's Meetings program and the public, the free concert series was a huge success. The concerts included:

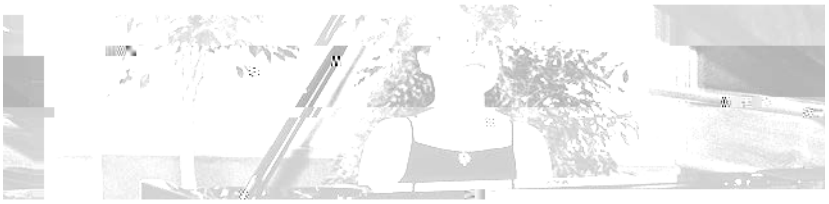
May 6	Karen Gomyo, violinist
May 20	Adam Neiman, pianist; Stefan Malenkovich, violinist; Ani Aznavoorian, cellist
May 27	Margarita Shevchenko, pianist
August 19	Julia and Irina Elkina, duo piano
August 26	Randall Scarlata, baritone and accompanist
September 9	Makoto Nakura, marimbist
September 16	Eric Johnson, jazz guitarist, with band
October 28	Viviane Hagner, violinist
November 11	Mark Ptashne (CSHL Board of Trustee Member), violinist

illenni C l ral Serie

In addition to the concert series, the Millennium Cultural Series brought several art events to the Laboratory for the year. Dale Chihuly, famed glass sculptor, presented a lecture on May 2 titled "Chihuly on Chihuly: The Jerusalem Project." The lecture, cohosted by the Hecksher Museum of Art, examined the sculptor's year of work in Israel. The Laboratory's second out-

Stefan Malenkovich, violinist; Ani Aznavoorian, cellist; Adam Neiman, pianist





Margarita Shevchenko

First ow to : Bruce Stillman, James Watson, Harry Wozniak, Frank Carberry
Second ow: Michael Riggs, G. Morgan Browne, Madeline Wisnowksi, David Spector
Third ow: Steven Tang, Linda Rodgers, Marlene Rubino, Patricia Hinton-Stenko
Fourth ow: Andrea Stephenson, Lisa Manche, Bruce Fahlbusch

La ra r E . ees

n - er Ser ice

On June 29th, employees celebrating milestone anniversaries with the Laboratory were honored at a special poolside dinner at Robertson House, on the Banbury Center property. Congratulations to all! Honorees included:

30 Years	Madeline Wisnewski
20 Years	Bruce Fahlbusch, Michael Riggs, Linda Rodgers, Marlene Rubino and Andrea Stephenson
15 Years	G. Morgan Browne, Frank Carberry, Patricia Hinton-Stenko, Lisa Manche, David Spector, Wanda Stolen, Steven Tang and Harry Wozniak

A ar an r n r

I was honored to be elected to the National Academy of Sciences (NAS) in May, 2000. Membership in the Academy is one of the highest honors a scientist can receive from an American organization.

C an e in A ini ra i e S a

Annette Gangitano joined us this year as the Executive Director of the Cold Spring Harbor Laboratory Association. Annette came to the Laboratory from a position with the firm of J&W Seligman.

Jeff Picarello joined us as the Director of Public Affairs. Jeff formerly worked at the C.W. Post Campus of Long Island University, where he was Director of Media Affairs.

ra a e S en epar re

The following graduate students left Cold Spring Harbor Laboratory in 2000:

Eric Gillitzer	Julia Polyakova	Beth Trumbull
Tina Gumienny	Alex Rai	Helena (Xiaohong) Yang
Susan Harrington	Bjorn Schumacher	Lee Zou
Shirly Pinto	Setareh Sepehri	

C ncl in Re ar

Constant change has been the theme at Cold Spring Harbor for much of its history, and this past year has been no exception. This dynamism, coupled with results emerging from the various genome projects, has opened new doors and revealed tremendous opportunities for biology and biomedicine, possibilities that were unheard of when I first came to Cold Spring Harbor Laboratory 21 years ago. It is time once again for this institution to rise to the challenges before us, enjoying, but not resting on, our significant past achievements.

Cold Spring Harbor Laboratory is a unique research and educational institution, more like an advanced research university now than ever before. More than many other universities, we have the flexibility to rapidly adapt to the fast pace of modern science. However, to remain at the leading edge of research in areas such as cancer and neuroscience, we will require major new infrastructure, significant new funding, dedication, and much energy from our already efficient and busy staff. This institution has never shied away from a challenge, and I am confident that with the right help, we will go on to an even brighter future.

A ril 2001 **, r ce S a**